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TETRAHEDRON: *ASYMMETRY*

NMR determination of absolute configuration of α-acyloxy ketones

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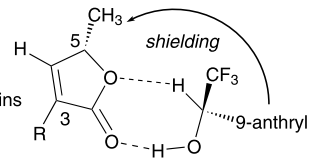
Abstract—Determination of the absolute configuration of several acyclic α-acyloxy-ketones, and δ-ketobutanolides, in the presence of a chiral solvating agent, by low temperature and low concentration ^{1}H NMR analysis, is reported.

The absolute configuration of non-derivatizable stereogenic centers (of both natural products and synthetic compounds) are difficult to determine. Circular dichroism[1] and chiral chromatographic methods[2] (e.g. HPLC, GC) have been employed for such a task, but a more readily usable technique such as NMR analysis is preferable because the equipment is accessible (400 MHz NMR spectrometers are commonly used) and the experiments are rapid, inexpensive and can be performed with small quantities of material. We have recently shown that when racemic 5-methylfuran-2(5*H*)one **2** was analyzed by ^{1}H NMR in $CDCl_3$ solution at 223 K in the presence of 4 equiv. of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol **1** (TFAE), we were pleased to observe that both the methyl group and H-5 appeared as two signals (δ 1.378/1.331 and 5.095/5.054 ppm, respectively) corresponding to the (*R*,*S*)- and (*R*,*R*)-solvates.[3]

Furthermore as expected, the chemical shift of the methyl group of the (*R*,*S*) solvate is observed upfield to that of the (*R*,*R*) solvate, as shown by selective irradiation of the H-5 signal, due to the shielding effect of the aromatic rings. This was predicted by our model.[3] Several natural 5-methylfuran-2(5*H*)ones bearing a substituent at the 3 position (e.g. annonaceous acetogenins[4]) were analyzed and the absolute configuration of their butenolide moiety was determined using this method (Scheme 1). We then decided to check if δ-ketobutanolides could also be analyzed by our method. Compounds **3** and **4** were first prepared as already reported from (*S*)-glutamic acid[5] and then analyzed in the presence of (*R*)- and (*S*)-TFAE **1**. When **3** and **4** (0.3 mg, 1 μmol and 1.7 μmol, respectively) were separately mixed with 17 and 21 equiv. of (*R*)-**1**, respectively, at 213 K in $CDCl_3$ and after irradiation at δ 2.25 ppm, we observed a singlet for H-5 of **3** and **4** at δ 4.738 and 4.760 ppm, respectively.

When **3** and **4** were analyzed under the same conditions, with 17 and 21 equiv. of (*S*)-**1**, respectively, the signals appeared at δ 4.775 and 4.786 ppm (corresponding to $\Delta\delta_{R-S} = -0.037$ and -0.026, respectively). The signs of the differences of chemical shifts ($\Delta\delta_{R-S} < 0$) are in accord with the model showing a first hydrogen bond between the OH of **1** and the lactone carbonyl of **3** (or **4**), and a second hydrogen bond[6] between the $C_\alpha H$ of **1** and the ring oxygen of the lactone (Scheme 2). Thus,

R = H : **2**
R = functionalized alkyl chain : acetogenins



Scheme 1.

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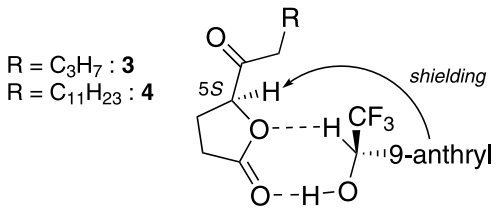
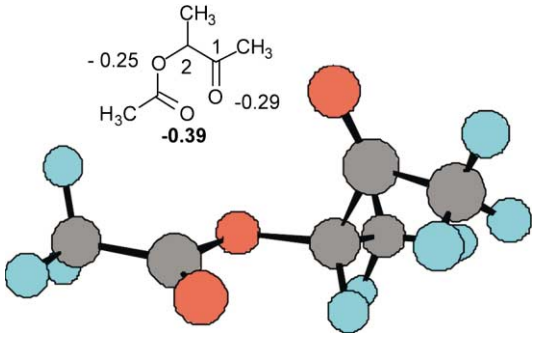


Scheme 2.

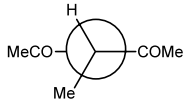
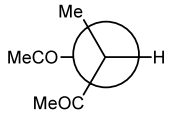
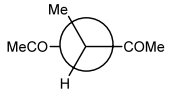
the 9-anthryl group of (*R*)-**1** in the solvates has a more pronounced shielding effect on H-5, while there is less (or no) effect on this hydrogen with (*S*)-**1**. This implies that these ketones have (*S*) absolute configuration, as is known from their stereospecific synthesis from (*S*)-glutamic acid. We then decided to study the extension of this method to acyclic derivatives of α-hydroxy-ketones, compounds possessing ester and ketone functionalities. NMR differentiation of diastereomeric complexes of chiral substrates with a chiral reagent could be expected if a conformational preference of the substrate exists and there is some preferred complexation site in the substrate. To estimate this we analyzed the simplest model shown in Scheme 3, by semiempirical method (PM3).

Conformational analysis around three single bonds (CO–O, O–C2 and C2–C1) was studied. Rotation around the last two bonds (the first one being discounted because of preferences[7]) produces six conformers (Table 1) whose major one possessing C2-H *gauche* to the ester O–CO and the ketone carbonyl *trans* with respect to C2–H. In this dominant conformer the two carbonyl groups are close to each other and both can be involved in hydrogen bonding (see Scheme 3), without incurring a high energetic barrier. Indeed, these calculations confirm, as expected, free rotations around these three single bonds of the molecule. Furthermore, according to PM3 (as well as pK_a considerations), the carbonyl oxygen of the ester function is more electronegative than the carbonyl oxygen of the ketone (–0.39 versus –0.29 (Scheme 3)). Thus, we can expect a pseudocyclic structure of the complex with a first hydrogen bond between the hydroxy group of **1** and the ester carbonyl and a second hydrogen bond between $C_\alpha H$ of **1** and the ketone carbonyl. The orientation of the 9-anthryl ring in this conformation should deter-



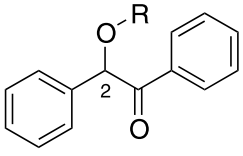
Scheme 3.

Table 1. Main conformations energies (PM3 data in kcal/mol) of the model depicted in Scheme 3

Conformation around O-C1	Conformation around C1-C2 *trans* (C=O with C1-H)	Conformation around C1-C2 *cis* (C=O with C1-H)
gauche1 	0.79	0.53
anti 	1.71	3.03
gauche2 	0	1.06

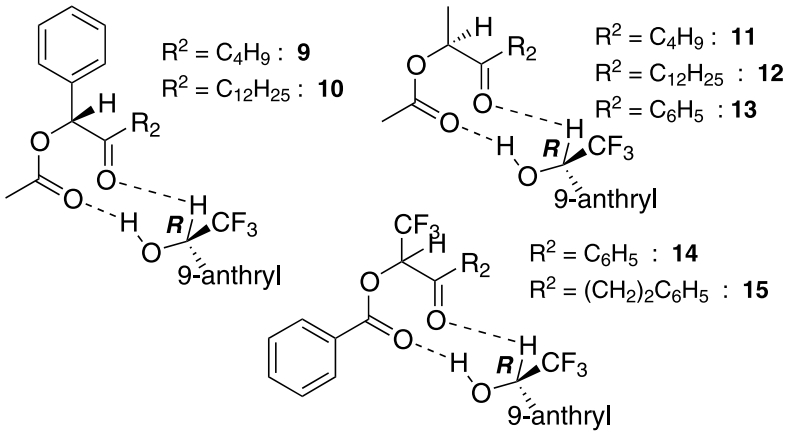
mine the overall chemical shift of H-2 of the substrate and this can preclude NMR determination of absolute stereochemistry of such substrates. Thus, racemic benzoin acetate **5**, -pivalate **6**, -benzoate **7**, as well as the *tert*-butyldimethylsilyl ether of benzoin, **8** were readily prepared (Scheme 4).

NMR experiments were then carried out by adding pure (*R*)- or (*S*)-TFAE **1** to a $CDCl_3$ solution (1.6–3.2 mM) of the racemic analyte, and the spectra recorded at 213 K. The signal for H-2 of benzoin acetate **5** (0.5 mg, 1.9 μmol, with 11 equiv. of (*S*)-**1**, 5.8 mg) appeared as two singlets integrating to 1:1 at δ 6.816 and 6.777 ppm. When benzoin pivalate **6** was analyzed under the same conditions, the signal for H-2 also appeared as two singlets integrating to 1:1 at δ 6.729 and 6.690 ppm. However, benzoin benzoate **7**, under the same conditions, showed a broad singlet at 6.996 ppm, whereas with 19 equiv. of (*S*)-**1**, two singlets integrating to 1:1 at δ 6.978 and 6.969 ppm now appeared. When the *tert*-butyldimethylsilyl ether of benzoin **8** was analyzed with 16 equiv. of (*R*)-**1**, two singlets, integrating to 1:1 at δ 5.717 and 5.709 ppm, were observed. From these observations we can conclude that α-acetoxy ketones or α-pivaloyloxy ketones are best suited for analysis and e.e. determination by this method. However, the trialkylsilyl ethers of the corresponding α-hydroxy ketones could also be used. The α-acetoxy ketones **9** and **10** were prepared in 43 and 54% yield, respectively, from racemic and (*R*)-α-acetoxy mandelic acid chloride and the α-acetoxy ketones **11**–**13** were



R = $COCH_3$: **5**
R = $COC(CH_3)_3$: **6**
R = COC_6H_5 : **7**
R = $Si(CH_3)_2C(CH_3)_3$: **8**

Scheme 4.



Scheme 5.

prepared from racemic and (*S*)-α-acetoxy lactic acid chloride,[8] and the corresponding Grignard reagents[9] using a slightly modified published procedure[10] (Scheme 5). The results of the NMR experiments are summarized in Table 2. First, the racemic compounds **9**–**13** were analyzed with (*R*)-**1**, showing two signals for H-2. Then each enantioenriched product was analyzed with either (*S*)-**1** or (*R*)-**1**, under the same conditions. It is of note that for compounds **11**–**13**, irradiation at δ 1.33 ppm (45 dB) was required in order to suppress the coupling constant between the CH_3 and H-2 (thus giving singlets). In all cases, the analysis of the enantioenriched compounds[11] with either (*R*)- or (*S*)-**1** showed a single signal superimposable with one of the two signals obtained from the racemic compounds (when the same number of equivalents of reagent **1** is used (Fig. 1)).

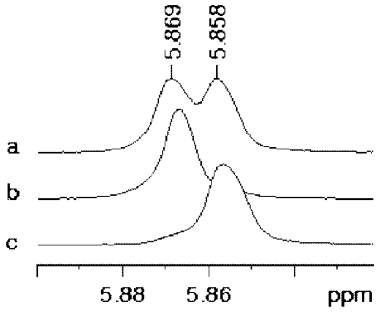


Figure 1. Partial ^{1}H NMR spectra: (a) (±)-**9** and 13 equiv. (*R*)-**1**; (b) (*R*)-**9** and 13 equiv. (*R*)-1; (c) (*R*)-**9** and 15 equiv. (*S*)-**1**.

From the above calculations, the first hydrogen bond should occur between the hydroxy group of **1** and the carbonyl group of the ester functions and the second hydrogen bond between the CαH of **1** and the carbonyl oxygen of the ketones (Scheme 5). The observed results are all in accord with this model, which predicted that for compounds **9** and **10** $\Delta\delta_{R,S} > 0$ (entries 1 and 2) is indicative that H-2 is on the same side than the CF_3 group in the solvate formed with (*R*)-**1**, and thus in accord with (*R*) absolute configuration of the stereogenic centers (through the CIP priority order), whereas for compounds **11-13**, $\Delta\delta_{R,S} < 0$ is indicative of (*S*) absolute configuration (entries 3–5).

We then studied the two racemic α-benzoyloxyketones **14** and **15** bearing a trifluoromethyl group.[12] Again we were pleased to observe that in the presence of 12 and 15 equiv. of (*R*)-**1**, respectively, two signals appeared, after decoupling of the fluorine atom, for H-2, at δ 6.389 and 6.368 ppm, and δ 5.601 and 5.590 ppm, corresponding to $\Delta\delta = \pm 0.021$ and ±0.011 for **14** and **15**, respectively (Table 2). By applying our model, we can predict that the signals appearing at higher field correspond to H-2 of the (*R*)-**14** and (*R*)-**15** compounds, whereas the downfield signals correspond to H-2 of the (*S*)-**14** and (*S*)-**15** enantiomers. In other words, $\Delta\delta_{R,S} < 0$ are in agreement with these predictions (these results are in accord with precedent results, but because of inversion of the CIP priority orders, the signs of $\Delta\delta_{R,S}$ are inverted compare to compounds **9** and **10**).

Table 2. $\Delta\delta$ H-2 of ketones **9**–**15** with either (*S*)- or (*R*)-**1**

Entry	Substrate	$\Delta\delta_{R,S}$ (*n* equiv. of **1**)	Absolute config. (ee)
1	**9**	+0.011 (13)	*R* (>96)
2	**10**	+0.012 (13)	*R* (>96)
3	**11**	−0.022 (18)	*S* (>96)
4	**12**	−0.024 (21)	*S* (>96)
5	**13**	−0.136 (24)	*S* (>96)
6	**14**	±0.021 (12)	– (0)
7	**15**	±0.011 (15)	– (0)

By applying the same model, as shown in Scheme 5, to compounds **5**–**8**, we can predict that the signals appearing upfield correspond to the (*S*,*S*) or (*R*,*R*) solvates, whereas the downfield signals correspond to the (*R*,*S*) or (*S*,*R*) solvates.

In conclusion, this study shows that our very efficient ^{1}H NMR method allows the determination of the absolute configuration of cyclic and acyclic α-acyloxyketones, as well as their e.e.s. The observed $\Delta\delta_{R,S}$ values are usually greater than 0.01 ppm (0.01–0.136

ppm), which is well above the experimental resolution and is similar to the differences in chemical shifts obtained with Mosher's esters.[13] Thus, we propose that in order to measure the e.e. of α-hydroxyketones, their corresponding acetates should be prepared and then analyzed by our method, instead of preparing the Mosher's esters at the risk of performing a kinetic resolution and thus obtaining false results. This technique extends the use of Pirkle's reagent[14] (currently employed for e.e. and absolute configuration determinations of cyclic compounds such as lactones[14] and lactams[15]) because of the crucial effect of *low temperature and low concentration*, allowing one to apply this method to other natural products as well.

Acknowledgements

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9. **Typical non-optimized procedure**: To a solution of carboxylic acid chloride (15 mmol) in THF (10 mL) at −78°C was added the corresponding Grignard reagent (17 mmol). After 3 h of stirring, the mixture was hydrolyzed with saturated NH_4Cl solution. The aqueous solution was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and evaporated. The crude mixture was purified by flash-chromatography (cyclohexane/EtOAc) to afford the corresponding ketones: **9** (43%), **10** (54%), **11** (25%), **12** (30%), **13** (10%).
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11. **Data for compound 9**: $[\alpha]_D=-191$ (*c* 0.75, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 7.39 (brs, 5H), 5.97 (s, 1H), 2.39 (m, 2H), 2.18 (s, 3H), 1.49 (m, 2H), 1.22 (sex., 2H, $J=7.2$ Hz), 0.81 (t, 3H, $J=7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 203.97, 170.18, 133.33, 129.18, 128.95, 128.13, 80.65, 38.30, 25.27, 21.99, 20.61, 13.59; **10**: $[\alpha]_D=-128$ (*c* 0.78, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 7.46 (brs, 5H), 6.03 (s, 1H), 2.45 (m, 2H), 2.24 (s, 3H), 1.56 (m, 2H), 1.27 (brs, 18H), 0.94 (t, 3H, $J=6.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 204.05, 170.24, 133.37, 129.27, 129.00, 128.19, 80.70, 38.66, 31.88, 29.58, 29.51, 29.35, 29.30, 29.20, 28.91, 23.25, 22.65, 20.68, 14.05; **11**: $[\alpha]_D=-30$ (*c* 1.09, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.08 (q, 1H, $J=7.1$ Hz), 2.45 (m, 2H), 2.12 (s, 3H), 1.55 (m, 2H), 1.38 (d, 3H, $J=7.1$ Hz), 1.34 (m, 2H), 0.90 (t, 3H, $J=7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 207.74, 170.28, 74.58, 37.85, 25.22, 22.22, 20.67, 16.09, 13.74; **12**: $[\alpha]_D=-20$ (*c* 0.71, $CHCl_3$) ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.09 (q, 1H, $J=7.1$ Hz), 2.45 (m, 2H), 2.13 (s, 3H), 1.57 (m, 2H), 1.39 (d, 3H, $J=7.1$ Hz), 1.26 (brs, 18H), 0.88 (t, 3H, $J=6.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 207.68, 170.25, 74.58, 38.15, 31.85, 29.56, 29.39, 29.33, 29.27, 29.12, 23.13, 22.62, 20.65, 16.09, 14.02; **13**, see: Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron*, **1999**, *55*, 2431–2440.
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